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Contrasting Effects of Lower Body Positive Pressure on Upper Airways Resistance and Partial Pressure of Carbon Dioxide in Men With Heart Failure and Obstructive or Central Sleep Apnea

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Objectives This study sought to test the effects of rostral fluid displacement from the legs on transpharyngeal resistance (R_{ph}), minute volume of ventilation (V_{min}), and partial pressure of carbon dioxide (PCO_2) in men with heart failure (HF) and either obstructive (OSA) or central sleep apnea (CSA).

Background Overnight rostral fluid shift relates to severity of OSA and CSA in men with HF. Rostral fluid displacement may facilitate OSA if it shifts into the neck and increases R_{ph}, because pharyngeal obstruction causes OSA. Rostral fluid displacement may also facilitate CSA if it shifts into the lungs and induces reflex augmentation of ventilation and reduces PCO_2, because a decrease in PCO_2 below the apnea threshold causes CSA.

Methods Men with HF were divided into those with mainly OSA (obstructive-dominant, n = 18) and those with mainly CSA (central-dominant, n = 10). While patients were supine, antishock trousers were deflated (control) or inflated for 15 min (lower body positive pressure [LBPP]) in random order.

Results LBPP reduced leg fluid volume and increased neck circumference in both obstructive- and central-dominant groups. However, in contrast to the obstructive-dominant group in whom LBPP induced an increase in R_{ph}, a decrease in V_{min}, and an increase in PCO_2, in the central-dominant group, LBPP induced a reduction in R_{ph}, an increase in V_{min}, and a reduction in PCO_2.

Conclusions These findings suggest mechanisms by which rostral fluid shift contributes to the pathogenesis of OSA and CSA in men with HF. Rostral fluid shift could facilitate OSA if it induces pharyngeal obstruction, but could also facilitate CSA if it augments ventilation and lowers PCO_2. (J Am Coll Cardiol 2013;61:1157–66) © 2013 by the American College of Cardiology Foundation

Sleep apnea occurs in approximately 50% of patients with heart failure (HF), where it is associated with increased mortality (1–3). There are 2 types of sleep apnea: obstructive (OSA) and central (CSA).

OSA is due to repetitive pharyngeal collapse during sleep that occurs when sleep-related loss in pharyngeal dilator muscle tone is superimposed upon a narrow pharynx (4).

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Pharyngeal narrowing can be due to fatty deposition in the neck or fluid retention in the pharyngeal mucosa. Increases

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Abbreviations and Acronyms

AHI = apnea-hypopnea index
BP = blood pressure
CSA = central sleep apnea
eGFR = estimated glomerular filtration rate
HF = heart failure
HR = heart rate
LBPP = lower body positive pressure
LVEF = left ventricular ejection fraction
LFV = leg fluid volume
NC = neck circumference
NT-proBNP = N-terminal of pro–B-type natriuretic peptide
NYHA = New York Heart Association
OSA = obstructive sleep apnea
PCO_2 = partial pressure of carbon dioxide
$PtcCO_2$ = transcutaneous PCO_2
R_{ph} = transpharyngeal resistance
SaO_2 = oxyhemoglobin saturation
V_{min} = minute volume of ventilation

in mucosal fluid volume around the pharynx may reduce pharyngeal cross-sectional area and increase transpharyngeal resistance (R_{ph}) (5). This may explain why OSA is more prevalent in patients with fluid retention, such as HF, than in the general population, despite lower body weight (1,6). It has also been shown that a reduction in overnight rostral fluid redistribution from the legs into the neck due to compression stockings during the daytime can attenuate OSA (7).

CSA is more prevalent in those with HF than in the general population (8), and is found predominantly in men for reasons yet to be elucidated (1). CSA during sleep occurs when partial pressure of carbon dioxide (PCO_2) falls below the apnea threshold due to hyperventilation (9). Several factors can contribute to hyperventilation and hypocapnia in HF patients with CSA, including respiratory control system instability due to increased chemosensitivity (10), pulmonary congestion (11), and arousals from sleep (9). Low cardiac output and prolonged circulation time might also play a role in the pathophysiology of CSA in HF, but these appear to contribute more to causing prolongation of the periodic breathing cycle than to precipitating central respiratory events (12,13). Unlike obstructive apneas and hypopneas, central apneas and hypopneas can sometimes be observed in HF patients with CSA while awake as part of Cheyne-Stokes respiration (14,15). Fluid retention may also play an important role in the pathogenesis of CSA by provoking hyperventilation and hypocapnia partly as a result of pulmonary irritant receptor stimulation by pulmonary congestion (11). In HF patients, PCO_2 is inversely proportional to pulmonary capillary wedge pressure (16), which is higher in patients with CSA than in those without CSA (12). In HF patients, nocturnal PCO_2 is also related inversely, and the frequency of central events, directly, to the amount of fluid displaced rostrally from the legs overnight (17). Under such conditions, increases in ventilation can decrease PCO_2 below the apnea threshold and trigger central apnea (9,18). Because augmented central respiratory drive stimulates both respiratory pump and pharyngeal dilator muscles (19), it is expected that the fluid shift into the lungs of HF patients may cause both an increase in ventilation and a lowering of R_{ph}, both of which will facilitate a drop in PCO_2. These observations suggest that fluid retention also plays a role in the pathogenesis of CSA. Fluid retention may explain, in part, why both types of sleep apnea are more common in HF patients than in the general population, why both types of sleep apnea can coexist in the same HF patient, and why the predominant type can change over time (20–22).

Our group previously showed in healthy, nonobese subjects that applying lower body positive pressure (LBPP) via medical antishock trousers causes rostral fluid displacement from the legs, which results in increases neck circumference (NC) and R_{ph}, decreases in pharyngeal caliber, and increases in pharyngeal collapsibility (5,23,24). The effects of rostral fluid shift from the legs by LBPP on NC, ventilation, PCO_2, and R_{ph} in patients with HF have yet to be determined. We, therefore, undertook the present study to test the hypotheses that the predominant effect of rostral fluid displacement from the legs by LBPP will be to induce pharyngeal obstruction in HF patients with OSA, as manifested by an increase R_{ph}, a reduction in minute volume of ventilation (V_{min}), and an increase in PCO_2, whereas in those with CSA, its predominant effect will be to augment respiratory drive as manifested by an increase in V_{min}, accompanied by reductions in R_{ph} and PCO_2.

Methods

Subjects. Inclusion criteria were men 18 to 85 years of age with HF due to ischemic or nonischemic dilated cardiomyopathy for ≥6 months, left ventricular ejection fraction (LVEF) ≤45%, in New York Heart Association (NYHA) classes I to III, and who were clinically stable without medication changes for ≥3 months. Exclusion criteria were acute decompensated HF, treated sleep apnea, tonsillar hypertrophy, and unstable angina, myocardial infarction, or cardiac surgery within the previous 3 months. Subjects' characteristics and medications were recorded before experiments. Echocardiography, including assessment of mitral regurgitation grades from 0 (none) to 4 (severe), estimated glomerular filtration rate (eGFR), and N-terminal of pro–B-type natriuretic peptide (NT-proBNP) levels were assessed within 3 months before the experiments. The Mallampati Score was assessed at the time of experiments (25). The protocol was approved by the Research Ethics Boards of University Health Network and Mount Sinai Hospital, and all subjects provided written consent before participation.

Polysomnography. All subjects underwent overnight polysomnography using standard techniques and scoring criteria for sleep stages and arousals (26,27). Thoracoabdominal motion was monitored by respiratory inductance plethysmography, and nasal airflow by nasal pressure cannulas. Oxyhemoglobin saturation (SaO_2) was monitored by oximetry. Apneas and hypopneas were defined as >90% and 50% to 90% reduction in tidal volume from baseline, respectively, lasting ≥10 s, and were classified as obstructive or central as

previously described (1). The frequency of apneas and hypopneas per hour of sleep (i.e., apnea-hypopnea index [AHI]) was quantified. Signals were recorded on a computerized sleep recording system (Sandman, Nellcor Puritan Bennett Ltd., Ottawa, Ontario, Canada) and scored by technicians blinded to the experimental data. Subjects were divided into an obstructive-dominant group (≥50% of events obstructive) and a central-dominant group (>50% of events central).

Lower body positive pressure, leg fluid volume, and neck circumference. With subjects lying supine, deflated medical antishock trousers (MAST III-AT, David Clark, Inc., Worcester, Massachusetts) were applied to both legs from the ankles to the upper thighs at the beginning of the baseline period. LBPP was applied by rapidly inflating the trousers to 40 mm Hg for 15 min, after which the trousers were deflated. We used this technique because we have shown that it is safe, induces rostral fluid shift, and unlike head-down tilting, does not alter posture, and therefore, does not cause posture-related alterations in upper airway geometry that could confound interpretation of the influence of fluid shifts on R_{ph}. Total fluid volume of both legs was measured using a bioimpedance spectrum analyzer (model 4200, Xitron Technologies, Inc., San Diego, California) (5,7,17,23,24,28–30). Two pairs of electrodes were applied to each leg: 1 pair to the upper thigh and the other to the ankle. This well-validated technique (31,32) uses impedance to electrical current within a body segment to measure its fluid content. A strain gauge plethysmograph (EC4, D.E. Hokanson, Inc., Bellevue, Washington) (33) was then wrapped around the neck above the cricothyroid cartilage and secured in place with tape to measure changes in NC during the experiments (5,23,24).

Pharyngeal resistance. After application of local anesthesia using a 10% lidocaine spray to the nares and the oropharynx, 2 open catheters were introduced into 1 nostril. The first catheter was advanced to the back of the nose, then withdrawn 0.5 cm to the choanae for measurement of nasopharyngeal pressure. The second catheter was advanced beyond the soft palate and base of the tongue to as far as the subjects could tolerate without gagging or discomfort, or to 18 cm from the nares, whichever was reached first, for measurement of hypopharyngeal pressure (5,34,35). The catheters were secured with tape to the upper lip and remained in place throughout the experiments. Each catheter was connected to a differential pressure transducer (Validyne MP45, Validyne Engineering, Northridge, California). These pressures were referenced to pressure measured inside a face mask. Flow was measured using a pneumotachograph (Hans Rudolph Model 4700, Hans Rudolph, Inc., Kansas City, Missouri) connected to a tightly fitting face mask. Pressure and flow signals were amplified and fed through an analog-to-digital converter, and then stored in a computer for later analysis. Transpharyngeal pressure gradient was calculated as the difference between hypopharyngeal and nasopharyngeal pressures, and R_{ph} was determined by dividing this by simultaneously measured airflow (35). Two to three milliliters of compressed air were injected through the proximal port of the catheters to clear secretions from the catheter tips as required.

Blood pressure, heart rate, PCO_2, and minute volume of ventilation. Systolic and diastolic blood pressures (BP) were recorded every 5 min using an automated oscillatory device applied to the upper arm (BPM-200: BpTRU Medical Devices Ltd., Coquitlam, British Colombia, Canada). Heart rate (HR) was measured during BP measurements. Transcutaneous PCO_2 ($PtcCO_2$) was recorded with a capnograph (Microgas 7650, Linde, Basel, Switzerland) placed on the surface of the chest and calibrated against test gases at the beginning of each study. Tidal volume and respiratory rate were monitored continuously by a respiratory inductance plethysmograph (Respitrace, Ambulatory Monitoring, Inc., Ardsley, New York) calibrated against a spirometer. V_{min} was calculated from the averaged tidal volume multiplied by respiratory rate per minute.

Experimental protocol. A randomized double crossover design was employed. Experiments were performed with subjects awake, and lying supine with their head and neck in the neutral position supported by a small pillow. Subjects were instructed to breathe normally through their noses.

Following a 5-min baseline period, subjects were randomized to either LBPP or a control period for the next 15 min. Subjects were then seated upright for 30 min as a washout period. They then underwent a second baseline period, after which they were crossed over to the other arm of the study for 15 min. To ensure subjects remained awake throughout studies, the sleep and/or wake state was assessed by electroencephalogram, and an electrooculogram and submandibular electromyogram were recorded. Measurements of leg fluid volume (LFV), BP, HR, V_{min}, and $PtcCO_2$ were made at the end of each baseline period, and at 5-min intervals during LBPP and control periods.

Data analysis. During each 30-s period, the greatest transpharyngeal pressure gradient and corresponding airflow were determined to calculate R_{ph}. Then, the R_{ph} values from each 30-s period were averaged over 5 min of the baseline period and 15 min of the LBPP and control periods. NC and V_{min} were averaged over the 5-min baseline period and the 15-min LBPP and control periods. For LFV, BP, HR, and $PtcCO_2$, values obtained at the end of each baseline, the LBPP and control periods were used for analysis.

Data are presented as mean ± SD or median (interquartile range), unless indicated otherwise. For comparisons of subjects' characteristics between obstructive- and central-dominant groups, Student *t*-test for normally distributed continuous variables, Mann-Whitney *U* test for non-normally distributed variables, and chi-square or Fisher's exact test for nominal variables were used. Within each group, 2-way repeated-measures analysis of variance, followed by a post hoc analysis with Bonferroni correction for multiple comparisons, was used to compare values obtained during the baseline and either LBPP or control periods.

Changes (Δ) from baseline to the LBPP period (i.e., values during LBPP − values at baseline) were then compared between the obstructive- and central-dominant groups using analysis of covariance to take into account any potential corresponding changes during the control period. Relationships between variables were examined by Pearson correlation coefficient. A 2-sided p value <0.05 was considered significant. Statistical analyses were performed by SPSS version 17.0 (SPSS Inc., Chicago, Illinois).

Results

Characteristics of the subjects. We recruited 28 men with HF: 18 in the obstructive-dominant group and 10 in the central-dominant group. Characteristics of these subjects are shown in Table 1. The central-dominant group had a significantly greater degree of mitral regurgitation, higher NT-proBNP level, and right ventricular systolic pressure, as well as shorter mitral inflow deceleration time compared with the obstructive-dominant group. However, there were no significant differences in other characteristics between the 2 groups. At the time of the experiments, none of the subjects had physical findings indicative of pulmonary edema. All subjects remained awake during studies, and neither periodic breathing nor Cheyne-Stokes respiration was observed in any of them during this time.

Effects of LBPP within groups. In the obstructive-dominant group, all variables remained stable during the control period compared with baseline (Table 2). Similarly, baseline values before the LBPP period did not differ significantly from baseline values before the control period. However, during the LBPP period, LFV decreased and NC increased significantly, and those changes were significantly greater than those during the control period ($p < 0.001$ for both). In addition, during the LBPP period, R_{ph} increased, V_{min} decreased, and PCO_2 increased significantly compared with baseline, and these changes were significantly greater than those during the control period ($p = 0.002$, $p = 0.003$, and $p = 0.046$, respectively).

In the central-dominant group, all variables also remained stable during the control period, and baseline values before the LBPP period did not differ significantly from baseline values before the control period (Table 2). During the LBPP period, LFV decreased and NC increased significantly, and those changes were significantly greater than those during the control period ($p < 0.001$ and $p = 0.004$, respectively). During the LBPP period, R_{ph} decreased, V_{min} increased, and PCO_2 decreased significantly compared with baseline, and these changes were significantly greater than those during the control period ($p = 0.005$, $p = 0.005$, and $p = 0.001$, respectively). No subject experienced any dyspnea or other side effects during the experiments.

Comparisons between obstructive- and central-dominant groups. As shown in Table 3, changes from the control to the LBPP period for systolic and diastolic BP, HR, LFV, and NC did not differ between the 2 groups. However, there were contrasting responses of R_{ph}, V_{min}, and $PtcCO_2$ to LBPP between the 2 groups: R_{ph} increased, V_{min} decreased, and $PtcCO_2$ increased in the obstructive-dominant group,

Table 1 Characteristics of the Subjects

Characteristics	Obstructive-Dominant (n = 18)	Central-Dominant (n = 10)	p Value
Age, yrs	52.7 ± 10.7	60.2 ± 12.3	0.104
Height, cm	174.8 ± 9.3	171.0 ± 5.5	0.250
Weight, kg	98.2 ± 24.9	91.0 ± 15.5	0.416
BMI, kg/m^2	31.8 ± 6.5	31.1 ± 5.1	0.770
Neck circumference, cm	42.5 ± 4.0	42.3 ± 2.4	0.892
AHI, events/h	35.2 ± 21.7	43.8 ± 26.1	0.355
Mallampati score	3.0 (1.0)	2.5 (1.3)	0.555
Ischemic pathogenesis	7 (39)	5 (50)	0.698
NYHA class	2.0 (1.3)	3.0 (1.0)	0.226
LVEF, %	29.9 ± 9.1	31.6 ± 8.3	0.643
MR grade	0 (2.0)	3.0 (1.3)	0.002
Mitral E/A velocity ratio*	1.0 ± 0.4	1.3 ± 0.6	0.080
Deceleration time, ms	208.3 ± 27.3	162.3 ± 28.2	<0.001
Right ventricular systolic pressure, mm Hg†	31.0 ± 6.3	39.1 ± 8.6	0.012
NT-proBNP, ng/l	1636.0 ± 1673.8	3883.5 ± 2354.5	0.007
eGFR, ml/min/1.73 m^2	74.3 ± 21.0	69.2 ± 20.8	0.544
Beta-blockers	17 (94)	10 (100)	1.000
ACE inhibitors/AT2 antagonists	16 (89)	10 (100)	0.524
Spironolactone	8 (44)	3 (30)	0.453
Thiazide or loop diuretics	12 (67)	7 (70)	0.856

Values are mean ± SD or n (%). *Data unavailable in 3 of the obstructive-dominant and 4 of the central-dominant groups due to atrial fibrillation. †Data unavailable in 1 subject in each group due to technical difficulties.

ACE = angiotensin-converting enzyme; AHI = apnea-hypopnea index; AT2 = angiotensin-2 receptor; BMI = body mass index; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

Table 2 Changes From Baseline to Control or LBPP Period Within Each Group

	Baseline	Control Period	Baseline	LBPP Period	p Value*
Obstructive-dominant (n = 18)					
Systolic BP, mm Hg	121.7 ± 24.9	121.1 ± 25.4	122.7 ± 25.4	125.6 ± 27.4	0.103
Diastolic BP, mm Hg	75.5 ± 13.7	74.8 ± 12.8	77.0 ± 15.1	77.8 ± 15.6	0.311
Heart rate, beats/min	68.1 ± 12.1	67.2 ± 11.2	67.6 ± 12.0	68.3 ± 13.0	0.217
LFV, l	9.97 ± 2.71	9.94 ± 2.71	9.93 ± 2.70	9.67 ± 2.64†	<0.001
NC, %	0	0.03 ± 0.46	0	0.57 ± 0.42†	<0.001
R_{ph}, $cmH_2O/l/s$	5.50 ± 3.89	5.21 ± 3.62	3.82 ± 1.87	7.02 ± 5.19†	0.002
V_{min}, l	7.5 ± 1.4	7.7 ± 1.4	9.2 ± 3.3	8.9 ± 3.3†	0.003
$PtcCO_2$, mm Hg	40.2 ± 4.6	40.3 ± 4.5	39.8 ± 3.3	40.5 ± 5.8†	0.046
SaO_2, %	97.3 ± 1.0	97.4 ± 0.9	97.4 ± 0.8	97.5 ± 0.8	0.579
Central-dominant (n = 10)					
Systolic BP, mm Hg	112.2 ± 19.2	114.0 ± 20.7	115.1 ± 18.4	116.8 ± 18.0	0.944
Diastolic BP, mm Hg	70.3 ± 12.2	69.6 ± 11.4	71.3 ± 11.2	72.8 ± 13.2	0.343
Heart rate, beats/min	67.1 ± 11.3	66.4 ± 10.1	65.5 ± 10.0	64.8 ± 9.8	0.934
LFV, ml	8.07 ± 1.46	8.07 ± 147	8.05 ± 1.38	7.80 ± 1.34†	<0.001
NC, %	0	0.07 ± 0.39	0	0.50 ± 0.36†	0.004
R_{ph}, $cmH_2O/l/s$	4.69 ± 2.97	5.13 ± 2.60	5.96 ± 3.49	4.88 ± 2.60†	0.005
V_{min}, l	8.1 ± 2.6	7.9 ± 2.0	7.6 ± 2.8	8.7 ± 3.0†	0.005
$PtcCO_2$, mm Hg	37.6 ± 6.7	38.5 ± 6.2	39.4 ± 5.8	38.0 ± 5.7†	0.001
SaO_2, %	97.7 ± 1.1	97.9 ± 1.2	97.7 ± 0.9	97.7 ± 0.9	1.000

Values are mean ± SD. *p values for (time)*(treatment) interaction. †$p < 0.05$ versus baseline.
BP = blood pressure; LBPP = lower body positive pressure; LFV = leg fluid volume; NC = neck circumference; $PtcCO_2$, transcutaneous partial pressure of carbon dioxide; R_{ph} = pharyngeal resistance; SaO_2 = oxyhemoglobin saturation; V_{min} = minute volume of ventilation.

whereas R_{ph} decreased, V_{min} increased, and $PtcCO_2$ decreased significantly in the central-dominant group (Fig. 1).

Relationships between ΔLFV during LBPP and other variables. In the obstructive-dominant group, the greater the amount of fluid displaced from the legs during LBPP, the greater the increase in NC and R_{ph} during LBPP (Figs. 2A and 3A, respectively). However, there was no significant relationship between ΔLFV and either ΔV_{min} or $\Delta PtcCO_2$ during LBPP (Figs. 4A and 5A, respectively).

In the central-dominant group, there was no significant relationship between ΔNC and ΔLFV during LBPP (Fig. 2B). However, the greater the decrease in LFV during LBPP, the more pronounced the decrease in R_{ph}, the greater the increase in V_{min}, and the greater the decrease in $PtcCO_2$ (Figs. 3B, 4B, and 5B, respectively).

Relationship between ΔR_{ph} during LBPP and NT-proBNP levels. In the obstructive-dominant group, there was no significant relationship between ΔR_{ph} during LBPP and NT-proBNP levels ($r = -0.285$, $p = 0.251$). In addition, NT-proBNP levels did not correlate with ΔV_{min} or $\Delta PtcCO_2$ during LBPP ($r = 0.118$, $p = 0.640$, and $r = -0.284$, $p = 0.253$, respectively).

However, in the central-dominant group, there was a strong inverse relationship between ΔR_{ph} during LBPP and NT-proBNP levels ($r = -0.894$, $p < 0.001$). In addition, NT-proBNP levels correlated directly with ΔV_{min} and inversely with $\Delta PtcCO_2$ during LBPP ($r = 0.883$, $p = 0.001$, and $r = -0.715$, $p = 0.020$, respectively).

Table 3 Comparisons of Responses to LBPP Between Obstructive-Dominant and Central-Dominant Groups

	Obstructive-Dominant (n = 18)	Central-Dominant (n = 10)	p Value
ΔSystolic BP, mm Hg	2.9 ± 8.1	1.7 ± 4.6	0.526
ΔDiastolic BP, mm Hg	0.8 ± 4.9	1.8 ± 6.3	0.811
ΔHeart rate, beats/min	0.7 ± 3.9	−0.7 ± 1.8	0.849
ΔSaO_2, %	0.1 ± 0.1	−0.1 ± 0.4	0.671
ΔLFV, ml	−260.0 ± 104.5	−249.0 ± 88.8	0.489
ΔNC, %	0.57 ± 0.42	0.50 ± 0.36	0.781

Values are mean ± SD.
Abbreviations as Table 2.

Discussion

This study provides several insights relevant to the pathogenesis of OSA and CSA in men with HF. First, in the obstructive-dominant group, application of LBPP, which displaced 260 ml of fluid from the legs, increased NC and induced a degree of upper airway obstruction, reflected by an increase in R_{ph}. This was a physiologically significant effect because it was sufficient to reduce V_{min} and increase $PtcCO_2$. Second, in the central-dominant group, LBPP displaced a similar amount of fluid from the legs and resulted in an increase in NC similar to that in the obstructive-dominant group. However, in contrast to the obstructive-dominant group, LBPP induced a reduction in R_{ph} accompanied by an increase in V_{min}. These changes were physiologically significant because they were sufficient to reduce $PtcCO_2$ by 1.4 mm Hg; they might also be clinically significant because a decrease of this magnitude can induce central apnea during sleep in HF patients (9,18). These data suggested that a portion of the fluid displaced

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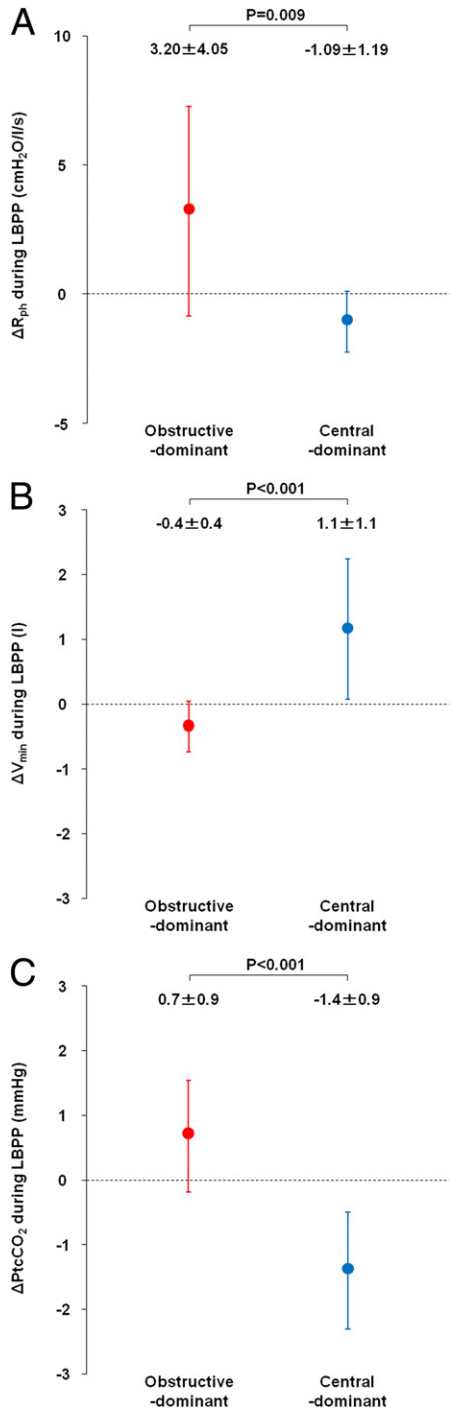

Figure 1 **Influence of Lower LBPP on R_{ph} and V_{min} in the Obstructive- and Central-dominant Groups**

In response to the lower body positive pressure (LBPP) in the obstructive-dominant group, transpharyngeal resistance (R_{ph}) **(A)** increased, minute volume of ventilation (V_{min}) **(B)** decreased, and transcutaneous PCO_2 ($PtcCO_2$) **(C)** increased, whereas in the central-dominant group, R_{ph} decreased, V_{min} increased, and $PtcCO_2$ decreased. Thus, LBPP caused opposite effects on R_{ph}, $PtcCO_2$, and V_{min} in the obstructive- and central-dominant groups. PCO_2 = partial pressure of carbon dioxide; $\Delta PtcCO_2$ = change in transcutaneous PCO_2; ΔR_{ph}, change in transpharyngeal resistance; ΔV_{min} = change in minute volume of ventilation.

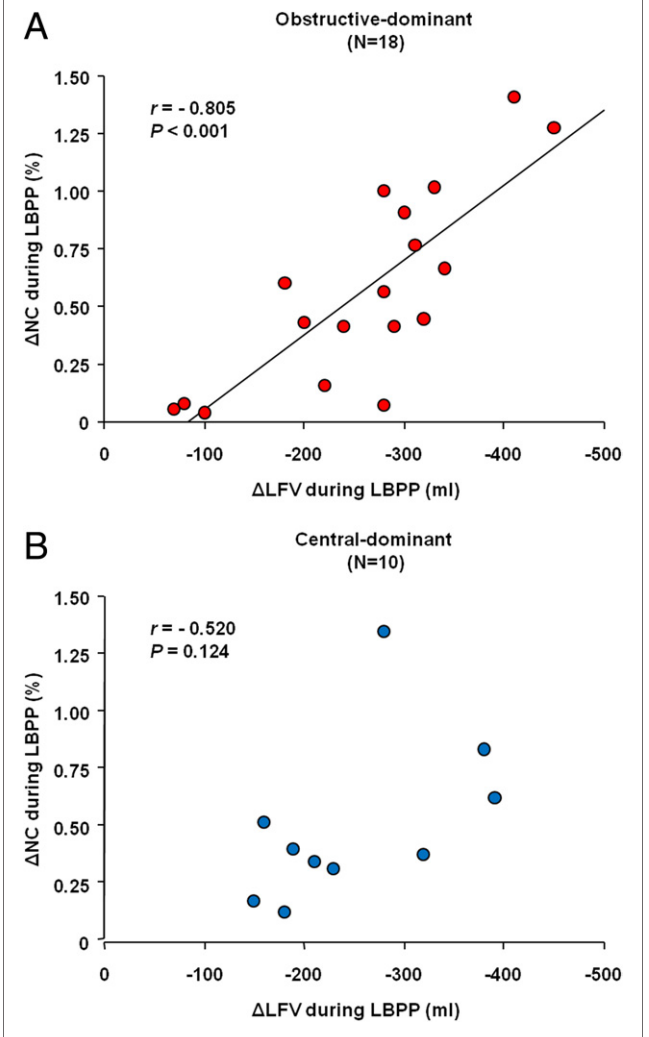

Figure 2 **Relationship Between ΔNC and ΔLFV in Response to LBPP in the Obstructive- and Central-Dominant Groups**

In the obstructive-dominant group **(A)**, the greater the reduction in leg fluid volume (LFV) during LBPP, the greater the increase in neck circumference (NC). However, in the central-dominant group **(B)**, there was no significant relationship between ΔLFV and ΔNC during LBPP. ΔLFV = change in leg fluid volume; ΔNC = change in neck circumference; other abbreviations as in Figure 1.

from the legs shifted into the lungs, stimulated pulmonary irritant receptors, and increased central respiratory drive. The observation that hyperventilation was accompanied by a decrease in R_{ph} indicated that such increased central respiratory drive activated both the inspiratory pump and pharyngeal dilator muscles simultaneously (19). Taken together, these data suggested that in patients with HF, rostral fluid displacement from the legs in obstructive-dominant patients behaved in a way that would predispose to upper airway obstruction during sleep, because it increased R_{ph}, which taken to the extreme, would result in complete pharyngeal occlusion. In contrast, in the central-dominant group, such fluid displacement behaved in a way that would augment respiratory drive and lower PCO_2, thus

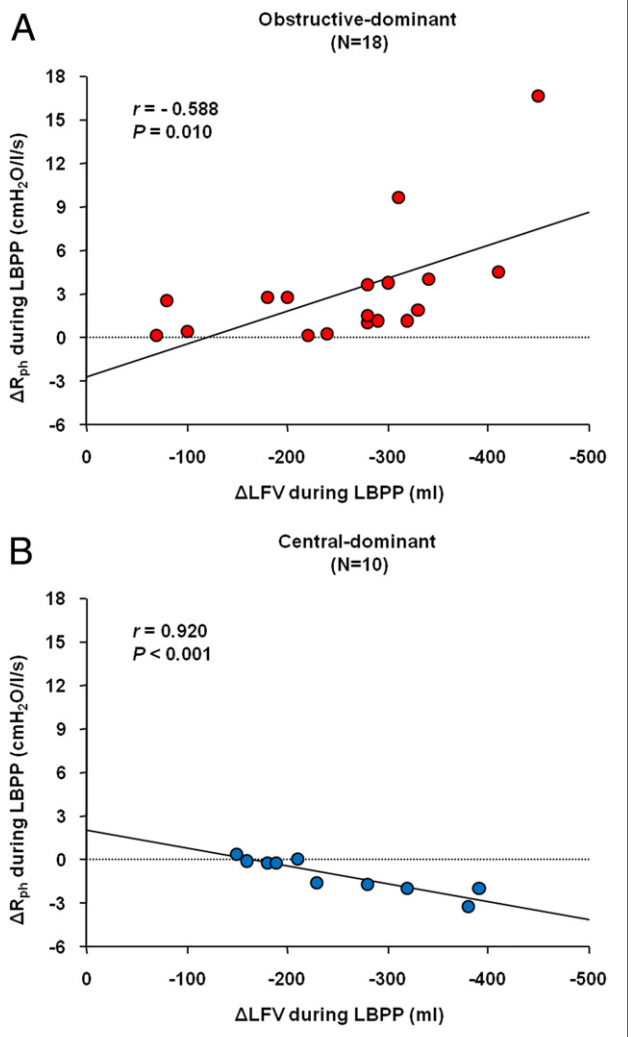

Figure 3 **Relationship Between ΔR_{ph} and ΔLFV in Response to LBPP in the Obstructive-and Central-Dominant Groups**

In the obstructive-dominant group **(A)**, the greater the reduction in LFV during LBPP, the greater the increase in R_{ph}. In contrast, in the central-dominant group **(B)**, the greater the reduction in LFV during LBPP, the greater the reduction in R_{ph}. Abbreviations as in Figures 1 and 2.

predisposing these patients to central apnea during sleep, because taken to the extreme, PCO_2 would fall below the apnea threshold. Accordingly, these findings extended those of our previous study in men with HF (17), by providing evidence of a differential response to rostral fluid shift that could predispose to OSA by inducing upper airway obstruction on the one hand (4,36) or to CSA by augmenting respiratory drive (37) on the other.

Compared with age- and weight-matched controls, OSA patients have higher pharyngeal resistance, and greater compliance and collapsibility during both wakefulness and sleep (38–41). Pharyngeal narrowing and increased R_{ph} can be due to an increase in surrounding soft tissue as a result of muscular hypertrophy, inflammation, and fat or fluid accumulation in the peripharyngeal tissues (4,36). The latter may be amenable to manipulation. For example, administration of systemic or topical vasoconstrictor agents that reduce peripharyngeal blood (i.e., fluid) volume to cats and humans increases pharyngeal cross-sectional area and reduces R_{ph} (42,43). In addition, the jugular veins lie adjacent to the lateral pharyngeal walls, and their distension can increase NC. Because NC generally correlates with AHI (44), outward expansion of the neck may be accompanied by inward displacement of the lateral pharyngeal walls, particularly behind the ramus of the mandible, which may impinge on the pharynx.

Our group previously showed that rostral fluid displacement from the legs by applying LBPP increases NC and R_{ph}

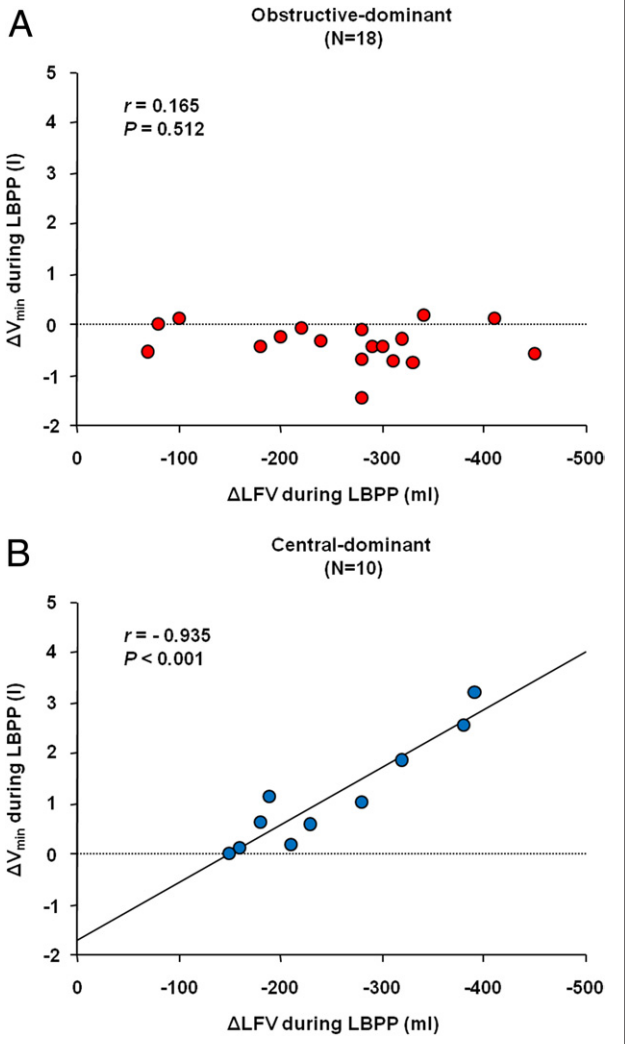

Figure 4 **Relationship Between ΔV_{min} and ΔLFV in Response to LBPP in the Obstructive- and Central-Dominant Groups**

In the obstructive-dominant group **(A)**, there was no significant relationship between ΔLFV and ΔV_{min} during LBPP. However, in the central-dominant group **(B)**, the greater the reduction in LFV during LBPP, the greater the increase in V_{min}. Abbreviations as in Figures 1 and 2.

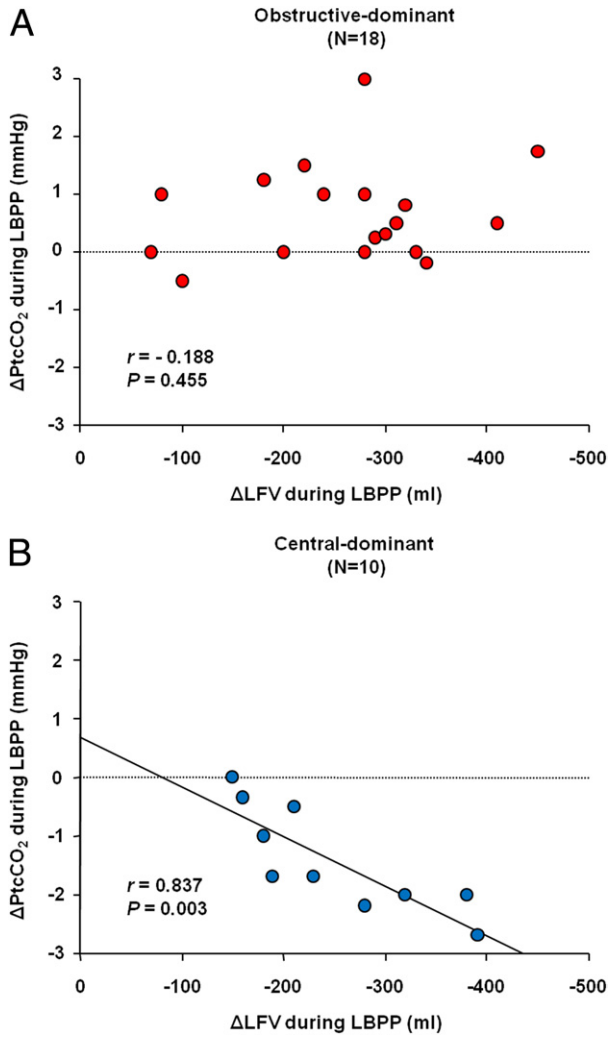

Figure 5 **Relationship Between $\Delta PtcCO_2$ and ΔLFV in Response to LBPP in the Obstructive- and Central-Dominant Groups**

In the obstructive-dominant group **(A)**, there was no significant relationship between ΔLFV and $\Delta PtcCO_2$ during LBPP. However, in the central-dominant group **(B)**, the greater the decrease in LFV during LBPP, the greater the decrease in $PtcCO_2$. Abbreviations as in Figures 1 and 2.

and decreases pharyngeal cross-sectional area and increases its collapsibility in healthy, nonobese subjects (5,23,24). There was also a strong relationship between the amount of fluid displaced spontaneously from the legs overnight and the overnight increase in NC and severity of OSA in nonobese, otherwise healthy men, in men with HF, and in subjects with hypertension or renal failure (17,28–30). Furthermore, the observation in both men with OSA and in patients with chronic venous insufficiency that use of venous compression stockings during the day reduced LFV, overnight LFV, and the AHI by approximately 35% provides proof that nocturnal rostral fluid shift plays a causative role in OSA (7). Bucca et al. (45) also reported, in an uncontrolled trial, that diuretic therapy increased pharyngeal caliber and reduced AHI in patients with decompensated diastolic HF. The observations from the present study that rostral fluid shift from the legs due to LBPP induces increases in both NC and R_{ph} in a dose-response manner in obstructive-dominant patients with HF provides evidence that one of the mechanisms through which rostral fluid displacement could cause OSA is by increasing peripharyngeal fluid accumulation and pharyngeal obstruction.

HF predisposes to CSA by provoking hypocapnia partly as a result of respiratory control system instability due to increased chemosensitivity (10), arousals from sleep (9), possibly increased circulation time, and nonchemical pulmonary irritant receptor stimulation by pulmonary congestion (11). In HF patients, PCO_2 is inversely proportional to pulmonary capillary wedge pressure (16). In 1 study, lowering wedge pressure by medical therapy and/or continuous positive airway pressure was associated with attenuation of CSA in patients with HF (12). More recently, we showed that overnight LFV is inversely proportional to PCO_2 during sleep and directly related to the severity of CSA (17). Accordingly, our findings provide novel evidence that nocturnal rostral fluid shift could predispose to CSA by increasing respiratory drive, by lowering R_{ph} and augmenting V_{min} sufficiently to decrease PCO_2 toward the apnea threshold. These findings are consistent with those in dogs and humans, in whom acute elevations in left atrial pressure provoked hyperventilation and reduced PCO_2 (16,46).

Despite their differing pathogenesis, men with HF can have both OSA and CSA simultaneously, and the predominant type can shift from obstructive to central in association with a decrease in PCO_2, an increase in circulation time, and deterioration in cardiac function, or vice versa (20–22). In a previous study, we observed a gradation from no sleep apnea to OSA to CSA with progressively greater overnight LFV shift (17). However, in the present study, we did not find any difference in ΔLFV between obstructive- and central-dominant groups in response to LBPP. One possible explanation for this discrepancy is that acute fluid shift induced by LBPP may consist mainly of intravascular fluid, whereas overnight fluid shift probably consists of both intravascular and extravascular components. Therefore, the volume of fluid displaced from the legs by LBPP may be less than the volume of fluid displaced overnight (17). In any case, the volume of fluid shifted was sufficient to increase R_{ph}, reduce V_{min}, and increase $PtcCO_2$ in the obstructive-dominant group, and to increase V_{min}, and to reduce R_{ph} and $PtcCO_2$ in the central-dominant group, probably due to pulmonary irritant receptor stimulation. Another possibility is that LBPP could have increased the venous return of CO_2, and if there was greater chemoreceptor reflex gain in the central-dominant patients than in the obstructive-dominant patients, there might have been greater augmentation of ventilation in the former cohort as a consequence (47). Although conceivable, we consider this unlikely, given the small volume of fluid (260 ml) displaced as a result of the acute application of LBPP, and therefore, the poten-

tially small increase of CO_2 returned venously relative to the total cardiac output that might have occurred.

The differing respiratory response to LBPP in the obstructive- and central-dominant groups may be related to differing basal cardiac loading conditions. For example, in HF patients, pulmonary capillary wedge pressure is higher in those with CSA than in those with OSA or with no sleep apnea (12). In keeping with that finding, we observed that in the central-dominant group, the degree of mitral regurgitation and right ventricular systolic pressure were much higher than those in the obstructive-dominant group. In addition, NT-proBNP levels were more than 2-fold higher than those in the obstructive-dominant group, with significant relationships between NT-proBNP level and indicators of increased respiratory drive in response to LBPP. NT-proBNP is released mainly from the ventricular myocardium in response to increased wall stress associated with volume and pressure overload. Therefore, taken together, greater mitral regurgitation, and higher right ventricular systolic pressure and NT-proBNP levels in the central-dominant group are indicative of greater left ventricular filling pressures, which suggests that these patients had more pulmonary congestion than those in the obstructive-dominant group (48,49). Accordingly, for a similar fluid shift from the legs into the heart, pulmonary congestion with stimulation of vagal irritant receptors, a consequent increase in V_{min}, and a decrease in PCO_2 would more likely occur in patients with higher levels of left ventricular filling pressures and NT-proBNP than in those with lower levels. The significant inverse relationship between NT-proBNP and ΔR_{ph} during LBPP supports this concept. However, because NT-proBNP levels were measured up to 3 months before the experiments, it is possible they could have changed by the time the experiments were performed; therefore, the significant relationships between NT-proBNP and ΔR_{ph}, ΔV_{min}, and $\Delta PtcCO_2$ during LBPP may have altered. Nevertheless, because our subjects had to be clinically stable and on stable medications for at least 3 months, these relationships are liable to be meaningful.

Study limitations. First, the experiments were conducted during wakefulness. It was not feasible for subjects to sleep uninterrupted with inflation and deflation of the trousers while simultaneously measuring R_{ph} with a tightly fitting facemask. Therefore, the findings of the present study may not be reproduced exactly during sleep. However, responses to fluid shift during sleep are unlikely to be qualitatively different, because we previously found strong relationships in HF patients between spontaneous overnight fluid shift and the overnight increase in NC and AHI in obstructive-dominant patients, and between spontaneous overnight fluid shift and PCO_2 during sleep, as well as the AHI in central-dominant patients (17). Second, because we studied men only, our findings may not be applicable to women with HF (24). Women were not studied because CSA is rare in women with HF (1). Because we did not measure activity of pharyngeal dilator muscles, we cannot be certain that activation of these muscles caused the fall in R_{ph} in response to LBPP in the central-dominant group. Third, we did not assess chemosensitivity; therefore, we could not assess the possible role of differing chemosensitivity on the ventilatory and R_{ph} responses to LBPP. Further studies will be required to determine whether LBPP has any effect on genioglossus activity that might affect R_{ph} or on venous return of CO_2 that might affect ventilation. Finally, due to technical limitations, we could not measure lung fluid volume to determine whether fluid movement into the lungs during LBPP was related to increased V_{min} and reduced R_{ph} in the central-dominant group.

Conclusions

The present study provides mechanistic evidence in favor of the concept that nocturnal rostral fluid shift can contribute to the pathogenesis of both OSA and CSA in men with HF. Our data suggest that in those in whom rostral fluid shift induces an increase in R_{ph}, susceptibility to OSA will increase, whereas in those in whom it induces an increase in respiratory drive with reductions in R_{ph} and PCO_2, susceptibility to CSA will increase. In the latter case, this susceptibility appears to be related to greater left ventricular filling pressure as evidenced by higher levels of NT-proBNP in the central-dominant group that would predispose them to pulmonary congestion in response to fluid loading. Our findings also have therapeutic implications because they raise the possibility that prevention of fluid accumulation in the legs during the daytime or rostral fluid shift at night, by, for example, cardiac rehabilitation (50), by wearing venous compression stocking (7) or intensifying diuretic therapy (45), may alleviate OSA or CSA in some men with HF. Further studies are needed to test these possibilities.

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